PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 126745200641	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/20007	International filing date *(day/month/year)* 21 July 2000 (21.07.2000)	Priority date *(day/month/year)* 22 July 1999 (22.07.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/70 and US Cl.: 514/47,50,51		
Applicant NEWBIOTICS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20 February 2001 (20.02.2001)	27 January 2003 (27.01.2003)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Howard V Owens Telephone No. 703-308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/20007

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-76 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 77-82, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-15, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 19

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 19 are so unclear that no meaningful opinion could be formed *(specify)*:

Because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. ____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 2-6,9,10,13,14 and 16-18	YES
	Claims 1,7,8,11, 12, 15 and 20-25	NO
Inventive Step (IS)	Claims 2-6,9,10,13,14 and 16-18	YES
	Claims 1,7,8,11,12,15 and 20-25	NO
Industrial Applicability (IA)	Claims 1-18 and 20-25	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 17 and 18 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The application, as originally filed, did not describe: a method for selectively inhibiting a cell via administration of an enzyme activated prodrug wherein an effective amount of a compound that diminishes intracellular thymidine or purine, or an effective amount of 6-mercaptopurein, thioguanine, or 2'-deoxycoformycin is additionally added.

Guidance is provided for the use of the prodrug to target certain enzymes, such as thymidylate synthase, however, there is no guidance in the specification on the use of additional agents such as 6-mercaptopurein, thioguanine, or 2'-deoxycoformycin along with a prodrug to produce a toxic effect in a pathological cell.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1, 7, 8,11,12, 15 and 20-25 lack novelty under PCT Article 33(2) as being anticipated by Powell et al., WO 99/06072.

Claims 1, 7, 8, 11, 12 and 15 are drawn to a method for selectively inhibiting a pathological cell by administering an effective amount of a substrate compound that is converted into a toxin in the cell by the activating enzyme, wherein the cell is characterized by overexpression of an endogenous, intracellular activating enzyme.

Claims 20 -25 are drawn to an assay method for compounds that are converted into a toxin which selectively inhibits a pathological cell.

Powell teaches administration of a prodrug to target enzymes that are overexpressed and affect hyperproliferative disease states such as inflammation, cancer or cellular apoptosis pp. (6, 7 and 9). Powell also teaches that an additional pharmaceutical agent may be added to the prodrug compound in a composition (p. 17, line 34).

Powell also teaches an assay method for the prodrug which selectively inhibits a pathological cell via activation of the compound by an intracellular enzyme (See examples 8 and 9).

Claims 1, 7, 8, 11, 12, 15 and 20-25 lack an inventive step under PCT Article 33(3) as being obvious over Powell et al., WO 99/06072.

Claims 1, 7, 8, 11, 12, and 15 are drawn to a method for selectively inhibiting a pathological cell by administering an effective amount of a substrate compound that is converted into a toxin in the cell by the activating enzyme, wherein the cell is characterized by overexpression of an endogenous, intracellular activating enzyme; moreover, the activating enzyme is overexpressed as a result of prior chemotherapy or loss of tumor suppressor function.

Claims 20 -25 are drawn to an assay method for compounds that are converted into a toxin which selectively inhibits a pathological cell.

Powell teaches administration of a prodrug to target enzymes that are overexpressed and affect hyperproliferative disease states such as inflammation, cancer or cellular apoptosis pp. (6, 7 and 9). Powell also teaches that an additional pharmaceutical agent may be added to the prodrug compound in a composition (p. 17, line 34).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Powell also teaches an assay method for the prodrug which selectively inhibits a pathological cell via activation of the compound by an intracellular enzyme (See examples 8 and 9).

Powell does not specifically teach that the overexpression is caused by either chemotherapy or loss of tumor suppressor function; however, the method of Powell encompasses the use of overexpressing enzymes associated with the clinical disease states of either cancer or cellular apoptosis. Whether the overexpressing is caused by chemotherapy or tumor suppressor function, one of skill in the art would have been motivated to administer a prodrug activated by an overexpressing enzyme given the prior art's use of activated prodrugs to treat hyperproliferative conditions such as cancer or cellular apoptosis. Chemotherapy and loss of tumor suppressor function are affects of cancer therapy. Since the prior art teaches the use of an enzyme activated prodrug for the treatment of cancer, the causation of the overexpressing enzyme is moot with regards to the use of the enzyme for the activation of the prodrug into a compound that is toxic for a pathogenic cell.

Claims 2 and 3 meet the criteria set out in PCT Article 33(2) & (4), because the prior art does not teach or fairly suggest the use of the dinitrogen heterocyclic compounds of the invention as prodrugs for activation by overexpressing enzymes; moreover, the use of these prodrugs would find industrial applicability in cancer therapy.

---------- NEW CITATIONS ----------
NONE